IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	) Novel Heterocyclically Substituted Amides, Their Preparation and Use
Lubisch et al.	)
Serial Number:	) Group Art Unit:
Filed:	) Examiner:

PRELIMINARY AMENDMENT

Box Patent Application
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

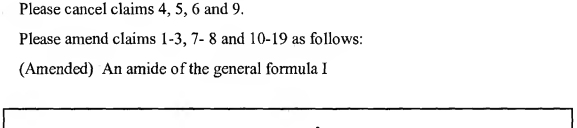
Dear Sir:

This is in reply to the Office Action of November 8, 2002.

Please cancel claims 4, 5, 6 and 9.

Please amend claims 1-3, 7- 8 and 10-19 as follows:

1. (Amended) An amide of the general formula I



and its tautomeric and isomeric forms, possible enantiomeric and diastereomeric forms, as well as possible physiologically tolerable salts, in which the variables have the following meanings:

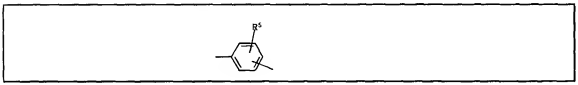
R^1 is selected from the group consisting of phenyl, naphthyl, quinolyl, pyridyl, pyrimidyl, pyrazyl, pyridazyl, imidazolyl, thiazole, quinazyl, isoquinolyl, quinoxalyl, thienyl, benzothienyl, benzofuranyl, furanyl, and indolyl, where the rings can be additionally substituted by up to 3 radicals R^5,

R^2 is selected from the group consisting of chlorine, bromine, fluorine, C_1-C_6-alkyl, C_1-C_6-alkenyl, C_1-C_6-alkynyl, C_1-C_6-alkylphenyl, C_1-C_6-alkenylphenyl,

C_1-C_6-alkynylphenyl, phenyl, NHCO-C_1-C_4-alkyl, $NHSO_2$-C_1-C_4-alkyl, -NHCOphenyl, -NHCO-naphthyl, NO_2, -O-C_1-C_4-alkyl and NH_2, where the aromatic rings can additionally carry one or two radicals R^5 and two radicals R^2 together can also be a chain -CH=CH-CH=CH- and thus form a fused benzo ring, which can be substituted by one R^5 and

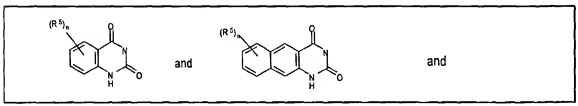
R^3 is -C_1-C_6-alkyl, which is branched or unbranched, and which can additionally carry an S-CH_3 radical or a phenyl, cyclohexyl, cycloheptyl, cyclopentyl, indolyl, pyridyl or naphthyl ring which is substituted by at most two radicals R^5, where R^5 is selected from the group consisting of hydrogen, C_1-C_4-alkyl, which is branched or unbranched, -O-C_1-C_4-alkyl, OH, Cl, F, Br, I, CF_3, NO_2, NH_2, CN, COOH, COO-C_1-C_4-alkyl, -NHCO-C_1-C_4-alkyl, -NHCO- phenyl, $-NHSO_2$-C_1-C_4-alkyl, $-NHSO_2$-phenyl, $-SO_2$-C_1-C_4-alkyl, $-(CH_2)_n-NR^{12}R^{13}$ and $-SO_2$-phenyl,

X is selected from the group consisting of a bond, $-(CH_2)_m-$, $-(CH_2)_m-O-(CH_2)_o-$, $-(CH_2)_o-S-(CH2)_m-$ [sic], $-(CH_2)_o-SO-(CH_2)_m-$, $-(CH_2)_o-SO_2-(CH_2)_m-$, -CH=CH-, -C≡C-, -CO-CH=CH-, $-(CH_2)_o-CO-(CH_2)_m-$, $-(CH_2)_m-NHCO-(CH_2)_o-$, $-(CH_2)_m-CONH-(CH_2)_o-$, $-(CH_2)_m-NHSO_2-(CH_2)_o-$, -NH-CO-CH=CH-, $-(CH_2)_m-SO_2NH-(CH_2)_o-$, -CH=CH-CONH- and



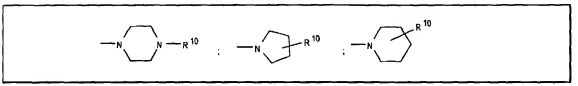
and in the case of CH=CH double bonds can be either the E or the Z form and

R^1-X together are also



Y is pyrimidine, and

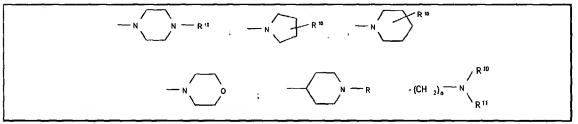
R^4 is selected from the group consisting of hydrogen, $COOR^6$, CO-Z, in which Z is NR^7R^8,



R^6 is hydrogen or C_1-C_6-alkyl, which is linear or branched, and which can be substituted by a phenyl ring which itself can additionally be substituted by one or two radicals R^9, and

R^7 is hydrogen or C_1-C_6-alkyl, which is branched and unbranched, and

R^8 is hydrogen or C_1-C_6-alkyl, which is branched or unbranched which can additionally be substituted by a phenyl ring which can additionally carry a radical R^9, and by



and

R^9 is selected from the group consisting of hydrogen, C_1-C_4-alkyl, which is branched or unbranched, -O-C_1-C_4-alkyl, OH, Cl, F, Br, I, CF_3, NO_2, NH_2, CN, COOH, COO-C_1-C_4-alkyl, -NHCO-C_1-C_4-alkyl, -NHCO-phenyl, -$NHSO_2$-C_1-C_4-alkyl, -$NHSO_2$-phenyl, -SO_2-C_1-C_4-alkyl and -SO_2-phenyl

R^{10} is hydrogen or C_1-C_6-alkyl, which is linear or branched, and which can be substituted by a phenyl ring which itself can additionally be substituted by one or two radicals R^9, and

R^{11} is hydrogen or C_1-C_6-alkyl, which is linear or branched, and which can be substituted by a phenyl ring which itself can additionally be substituted by one or two radicals R^9, and

n is a number 0, 1 or 2, and

m and o independently of one another are each a numeral 0, 1, 2, 3 or 4.

2. (Amended) An amide of the formula I as claimed in claim 1, where

R^3 is benzyl, $CH_2CH_2CH_2CH_3$, or $CH_2CH_2CH_2CH_2CH_3$ and

Y is pyrimidine and

R^4 is $CO\text{-}NR^7NR^8$ and

R^7 is hydrogen

R^8 is CH_2CH_2, $CH_2CH_2CH_2$, or $CH_2CH_2CH_2CH_2$ and

R^9 is hydrogen and

n is 0 or 1 and

all remaining variables have the same meanings as in claim 1.

3. An amide of the formula I as claimed in claim 1, where

R^3 is benzyl, $CH_2CH_2CH_2CH_3$, or $CH_2CH_2CH_2CH_2CH_3$ and

Y is pyrimidine and

R^4 is hydrogen and

R^9 is hydrogen

n is 0 or 1 and

all remaining variables have the same meanings as in claim 1.

7. A method of inhibiting cysteine proteases in a patient in need of such treatment comprising administering an effective amount of a compound of claim 1 to a patient in need of such treatment.

8. The method of claim 7 wherein the cysteine proteases are selected from the group consisting of calpains I and II and cathepsins B and L.

10. A method of treating neurodegenerative diseases and neuronal damage in a patient in need of such treatment comprising administering an effective amount of a compound of claim 1 to a patient in need of such treatment.

11. The method of claim 10 where the neurodegenerative diseases and neuronal damage is caused by ischemia, trauma or mass hemorrhages.

12. The method of claim 10 for the treatment of cerebral stroke and craniocerebral trauma.

13. The method of claim 10 wherein the disease is Alzheimer's disease or Huntington's disease.

14. The method of claim 10 wherein the disease is epilepsy.

15. A method of treating damage to the heart after cardiac ischemias, reperfusion damage after vascular occlusion, damage to the kidneys after renal ischemias, skeletal muscular damage, muscular dystrophies, damage which results due to proliferation of the smooth muscle cells, coronary vasospasm, cerebral vasospasm, cataracts of the eyes or restenosis of the blood vessels after angioplasty comprising administering an effective amount of a compound of claim 1 to a patient in need of such treatment.

16. A method of treating tumors and metastasis thereof comprising administering an effective amount of a compound of claim 1 to a patient in need of such treatment.